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Interaction of 4-hydroxyphenylpyruvate dioxygenase (HPPD) and atrazine alternative photosystem II (PS II) inhibitors for control of multiple herbicide–resistant waterhemp (*Amaranthus tuberculatus*) in corn

Research Article

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Abstract

The complementary activity of 4-hydroxphenylpyruvate dioxygenase (HPPD) inhibitors and atrazine is well documented, but the use of atrazine is restricted in some geographic areas, including the province of Quebec in Canada, necessitating the evaluation of atrazine alternatives and their interactions with HPPD inhibitors. The objectives of this study were to determine whether mixing HPPD inhibitors with atrazine alternative photosystem II (PS II) inhibitors, such as metribuzin and linuron applied PRE or bromoxynil and bentazon applied POST, results in similar control of multiple herbicide–resistant (MHR) waterhemp [*Amaranthus tuberculatus* (Moq.) Sauer] in corn (*Zea mays* L.). Ten field trials, five with herbicides applied PRE and five with herbicides applied POST, were conducted in Ontario, Canada, in fields infested with MHR *A. tuberculatus*. Isoxaflutole, applied PRE, controlled MHR *A. tuberculatus* 58% to 76%; control increased 17% to 34% with the addition of atrazine, metribuzin, or linuron at three of five sites across 2, 4, 8, and 12 wk after application (WAA). The interaction between isoxaflutole and PS II inhibitors, applied PRE, was additive for MHR *A. tuberculatus* control and biomass and density reduction. Mesotrione, tolpyralate, and topramezone, applied POST, controlled MHR *A. tuberculatus* 54% to 59%, 61%, and 44% to 45%, respectively, at two of five sites across 4, 8, and 12 WAA. The addition of atrazine, bromoxynil, or bentazon to mesotrione improved MHR *A. tuberculatus* control 29%, 34%, and 22%; to tolpyralate, improved control 2%, 20%, and 10%; and to topramezone, improved control 3%, 14%, and 8%, respectively. Interactions between HPPD and PS II inhibitors were mostly additive; however, synergistic responses were observed with mesotrione + bromoxynil or bentazon, and tolpyralate + bromoxynil. Mixing atrazine alternatives metribuzin or linuron with isoxaflutole, applied PRE, and bromoxynil or bentazon with mesotrione or tolpyralate, applied POST, resulted in similar or better control of MHR *A. tuberculatus* in corn.

Introduction

Multiple herbicide–resistant (MHR) waterhemp [*Amaranthus tuberculatus* (Moq.) Sauer] interference can cause substantial corn (*Zea mays* L.) yield losses and reduce net returns for producers in the United States and Canada. *Amaranthus tuberculatus* has been reported in 19 states of the United States and 3 Canadian provinces (Heap 2020). *Amaranthus tuberculatus* is a dioecious weed species that exhibits a rapid growth rate, high reproductive rate, delayed emergence, and an extended emergence pattern, all of which facilitate the evolution and spread of herbicide resistance among populations (Costea et al. 2005; Hartzler et al. 1999; Liu et al. 2012). A dioecious reproductive system allows *A. tuberculatus* to stack traits that confer resistance to multiple herbicide mechanisms of action (MOAs) (Jhala et al. 2020; Sarangi et al. 2017).

Herbicide resistance was first identified in *A. tuberculatus* in 1993 in a population that exhibited resistance to acetolactate synthase (ALS) inhibitors (Heap 2020). Resistance to six herbicide MOAs, including the synthetic auxins and ALS, photosystem II (PS II), protoporphyrinogen oxidase (PPO), 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), and 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors was reported in a Missouri MHR *A. tuberculatus* population in 2015 (Shergill et al. 2018). MHR *A. tuberculatus* is one of the most problematic weed species in row-crop production in North America and was the first to evolve resistance to HPPD inhibitors (Jhala et al. 2014; McMullan and Green 2011). Populations of MHR *A. tuberculatus* resistant to ALS, PS II, EPSPS, and PPO inhibitors have since been reported in Ontario, Canada (Benoit et al. 2019a). MHR *A. tuberculatus* continues to evolve resistance to herbicides that are extensively used for weed management in corn. When left uncontrolled, MHR *A. tuberculatus* can reduce grain corn yield by up to 74% (Steckel and Sprague 2004). Yield losses of up to 48% have been reported in Ontario (Soltani et al. 2009).

Herbicides that inhibit HPPD are widely used for weed management in corn production due to their broad-spectrum weed control and excellent crop safety. The HPPD inhibitors include isoxaflutole, mesotrione, topramezone, tembotrione, bicyclopyrone, and tolpyralate (Mitchell et al. 2001; USEPA 2007, 2015; van Almsick et al. 2013; Williams et al. 2011). They control many annual grass and broadleaf weed species, including herbicide-resistant biotypes (Grossman and Ehrhardt 2007; Pallett et al. 2001; Schulz et al. 1993). HPPD inhibitors can be applied PRE or POST in corn, permitting greater flexibility to various corn-cropping systems.

HPPD inhibitors and atrazine are often co-applied due to their complementary activity (Abendroth et al. 2006; Mitchell et al. 2001; Woodyard et al. 2009). Applying herbicides with distinct MOAs in a tank mixture can result in antagonistic, additive, or synergistic interactions. Colby's equation [$E = X + Y - (XY)/100$] (Equation 1), where E represents expected level of control of the products in combination, and X and Y represent the level of control of each herbicide applied independently, is used to determine the response of two herbicides in a tank mix (Colby 1967). When the herbicides are applied in combination and the observed level of control is less, equal, or greater than expected, the interaction can be classified as antagonistic, additive, or synergistic, respectively.

The HPPD- and PS II-inhibitor MOAs are distinct and complementary. Inhibition of the HPPD enzyme indirectly leads to a shortage of α-tocopherols, β-tocopherols, plastoquinone, and carotenoids (Collakova and DellaPenna 2001; Fritze et al. 2004; Lindblad et al. 1970). The PS II inhibitors readily displace plastoquinone from the Q_B binding site of the D1 protein in PS II, effectively blocking electron transport and causing reactive oxygen species (ROS) to accumulate (Hankamer et al. 1997; Hess 2000). Enhanced weed control from the co-application of an HPPD and a PS II inhibitor is due to (1) the lack of plastoquinone, which increases the binding efficiency of the PS II inhibitor to the D1 protein; and (2) enhanced levels of ROS due to lack of α-tocopherols, β-tocopherols, plastoquinone, and carotenoids, which quench ROS. Overall, this leads to photo-oxidative destruction of chlorophyll and destruction of photosynthetic membranes, giving rise to the characteristic white bleaching, or chlorosis, of young plant tissue followed by necrosis (Lee et al. 1997).

Complementary activity between HPPD inhibitors and PS II inhibitors has been reported for the control of susceptible and triazine-resistant redroot pigweed (*Amaranthus retroflexus* L.), Palmer amaranth (*Amaranthus palmeri* S. Watson), and *A. tuberculatus* (Hugie et al. 2008; Kohrt and Sprague 2017; Sutton et al. 2002; Woodyard et al. 2009). Woodyard et al. (2009) reported excellent control of a susceptible *A. tuberculatus* biotype and synergy between mesotrione and atrazine or bromoxynil applied POST. Visible control of a susceptible *A. palmeri* biotype from Nebraska was improved with the co-application of mesotrione + atrazine, bromoxynil, or metribuzin applied POST (Abendroth et al. 2006). Other studies have reported excellent control of MHR *A. tuberculatus* with HPPD + atrazine tank mixtures (Benoit et al. 2019b; Schryver et al. 2017; Vyn et al. 2006). Complementary activity between HPPD inhibitors and other PS II inhibitors such as bentazon and linuron has not been documented for control of *Amaranthus* species. Tank mixtures of HPPD inhibitors and PS II inhibitors are effective for control of MHR *A. tuberculatus* and MHR *A. palmeri*; however, reported interactions between HPPD inhibitors and PS II inhibitors can be specific to the HPPD inhibitor, *Amaranthus* species, and biotype resistance profile (Chahal and Jhala 2018; Hugie et al. 2008; Kohrt and Sprague 2017; Woodyard et al. 2009).

Current MHR *A. tuberculatus* control programs rely heavily on the mixture of HPPD inhibitors and atrazine applied PRE, POST, or PRE fb POST in corn. Of great concern to weed management practitioners is the restricted use of atrazine in some geographic areas. A comprehensive study on the mixture of HPPD inhibitors with alternative PS II inhibitors, applied PRE or POST, is needed to determine the effect on MHR *A. tuberculatus* control. Given the ability of *A. tuberculatus* to rapidly evolve resistance, rapidly reproduce, and competitively interfere with corn production, other PS II inhibitors complementary with the HPPD inhibitors need to be identified. It is hypothesized that PRE or POST herbicide tank mixtures containing HPPD inhibitors + PS II inhibitors will result in season-long control of MHR *A. tuberculatus* in corn. The objectives of these studies were to evaluate the interaction between HPPD inhibitors and a series of PS II inhibitors, applied PRE or POST, on MHR *A. tuberculatus* control in Ontario corn production.

Materials and Methods

Experimental Methods

Ten field trials were conducted in Canada during 2 yr (2019, 2020) at sites (S) on Walpole Island, ON (S2, S5) (42.561492°N, 82.501487°W), near Cottam, ON (S1, S3, S4) (42.149076°N, 82.683687°W), and near Port Crewe, ON (S6) (42.192390°N, 82.215453°W) (Table 1). The PRE study was conducted at S1, S2, S4, S5, and S6, and the POST study was conducted at S1, S2, S3, S4, and S5 (Table 1). Populations of MHR *A. tuberculatus* resistant to ALS, PS II, EPSPS, and PPO inhibitors were confirmed at all sites by treating separate quadrats with a POST application of imazethapyr (BASF Canada, 100 Milverton Drive Mississauga, ON, Canada) (100 g ai ha^{-1}) + Agral® 90 (Syngenta Canada, 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v) + urea ammonium nitrate (UAN 28-0-0, Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v), atrazine (Syngenta Canada) (1,500 g ai ha^{-1}) + Assist® oil concentrate (BASF Canada) (1% v/v), glyphosate (Bayer CropScience, 160 Quarry Park Boulevard SE, Calgary, AB, Canada) (900 g ae ha^{-1}), or fomesafen (Syngenta Canada) (240 g ai ha^{-1}), respectively, when plants were 10 cm in height. The percentage of resistant plants was calculated for each MOA by dividing the number of surviving *A. tuberculatus* plants in each quadrat at 3 wk after application (WAA) by the number of plants before herbicide application.

Sites were cultivated twice in the spring to prepare the trial area for planting. Glyphosate- and glufosinate-resistant corn was seeded in rows spaced 0.75 m apart at approximately 83,000 seeds ha^{-1} to a depth of 4 cm in late May to late June. The PRE study was designed as a two by four factorial. Factor 1 consisted of two levels of HPPD inhibitor: nontreated control and isoxaflutole, and Factor 2 consisted of four levels of PS II inhibitor: nontreated control, atrazine, metribuzin, and linuron. The POST study was designed

Table 1. Soil characteristics and multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* resistance profile of six field sites where 4-hydroxyphenylpyruvate dioxygenase (HPPD), photosystem II (PS II), and HPPD + PSII inhibitors were applied PRE and POST in Ontario, Canada, in 2019 and 2020.[a]

				Soil characteristics						Resistance profile[b]			
Site	Year	Location	Trial(s)	Classification	Sand	Silt	Clay	pH	OM	ALS	PS II	EPSPS	PPO
						%						%	
S1	2019	Cottam	PRE, POST	Sandy loam	70	21	9	6.0	2.6	97	34	N/A	N/A
S2	2019	Walpole	PRE, POST	Loamy sand	70	21	9	7.6	2.3	23	6	79	N/A
S3	2019	Cottam	POST	Sandy loam	70	21	9	6.0	2.6	97	34	N/A	N/A
S4	2020	Cottam	PRE, POST	Sandy loam	70	19	11	5.9	2.6	68	54	64	43
S5	2020	Walpole	PRE, POST	Sandy loam	76	15	9	7.8	2.5	54	30	96	17
S6	2020	Port Crewe	PRE	Clay loam	24	37	39	6.6	3.8	82	57	59	63

[a]Abbreviations: OM, organic matter; ALS, acetolactate synthase inhibitor; EPSPS, 5-enolpyruvylshikimate-3-phosphate synthase inhibitor; PPO, protoporphyrinogen oxidase inhibitor.
[b]Mean number of surviving plants *at 3 wk* after application divided by the number of plants treated within eight quadrats per mode of action.

Table 2. Herbicide active ingredient, trade name, and manufacturer for the study of 4-hydroxyphenylpyruvate dioxygenase (HPPD) and photosystem II (PS II) inhibitors applied PRE and POST for the control of multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* in Ontario, Canada, in 2019 and 2020.

Herbicide active ingredient[a]	Trade name	Manufacturer
Atrazine	Aatrex® Liquid 480	Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada
Bentazon	Basagran® Liquid Herbicide	BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada
Bromoxynil	Pardner	Bayer CropScience Inc., 160 Quarry Park Boulevard SE, Calgary, AB, Canada
Isoxaflutole	Converge Flexx Herbicide	Bayer CropScience Inc., 160 Quarry Park Boulevard SE, Calgary, AB, Canada
Mesotrione	Callisto® 480SC Herbicide	Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada
Tolpyralate	Shieldex™ 400SC Herbicide	ISK Biosciences Corporation, 740 Auburn Road, Concord, OH, USA
Topramezone	Armezon®	BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada

[a]Herbicide treatments with mesotrione included Agral® 90 (Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v); with tolpyralate included methylated seed oil (MSO Concentrate®) (Loveland Products, 3005 Rocky Mountain Avenue, Loveland, CO, USA) (0.5% v/v) and urea ammonium nitrate (UAN 28-0-0) (Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v); and with topramezone included Merge® (BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada) (0.5% v/v).

as a four by four factorial. Factor 1 consisted of four levels of HPPD inhibitor: nontreated control, mesotrione, tolpyralate, and topramezone, and Factor 2 consisted of four levels of PS II inhibitor: nontreated control, atrazine, bromoxynil, and bentazon. PRE and POST trials were arranged in a randomized complete block design with four replications separated by a 2-m alley. Plots were 8-m long and 2.25-m (3 corn rows) wide. The entire trial area was sprayed with glyphosate (450 g ae ha^{-1}), applied POST to 5 cm *A. tuberculatus*, including nontreated controls, to remove the confounding effect of EPSPS inhibitor– susceptible MHR *A. tuberculatus* biotypes and other weed species.

Herbicide treatments (Table 2) were applied using a CO_2-pressurized backpack sprayer calibrated to deliver 200 L ha^{-1} at 240 kPa. The sprayer was equipped with four 120-02 ultra-low drift nozzles (Pentair, 375 5th Avenue NW, New Brighton, MN, USA) spaced 50 cm apart, producing a spray width of 2 m. The PRE treatments were applied in mid-May to late June between corn planting and corn emergence. All PRE treatments received sufficient rainfall within 2 WAA for activation. POST treatments were applied when MHR *A. tuberculatus* reached an average 10 cm in height in mid-June to late July. POST trials at S1 and S3 were in the same field; therefore, they were temporally separated by applying herbicide treatments 2 d apart.

Data were collected on visible MHR *A. tuberculatus* control, density and biomass, visible corn injury, grain corn moisture content, and grain corn yield. Visible MHR *A. tuberculatus* control was evaluated on a 0% to 100% scale as a visual estimation of weed control based on plant chlorosis, necrosis, and reduction in height compared with the nontreated control within each replication, where 0% represented no herbicide injury and 100% represented complete plant death (Metzger et al. 2018). Visible MHR *A. tuberculatus* control was evaluated at 2, 4, 8, and 12 WAA for the PRE trial and at 4, 8, and 12 WAA for the POST trial. Density and biomass of MHR *A. tuberculatus* were determined at 4 WAA by counting and harvesting the plants within two randomly placed 0.25-m^2 quadrats in each plot. The aboveground biomass of the plants within each quadrat was determined by cutting the MHR *A. tuberculatus* at the soil surface; the plants were placed inside paper bags, kiln-dried for 3 wk to a consistent moisture, and then weighed using an analytical balance to obtain MHR *A. tuberculatus* biomass (g m^{-2}). Visible corn injury was assessed on a 0% to 100% scale at 1, 2, and 4 wk after emergence for the PRE trial and 1, 2, and 4 WAA for the POST trial; 0% represented no visible injury and 100% represented complete plant death. Grain corn yield (kg ha^{-1}) and moisture (%) were determined by harvesting two rows of each plot at maturity using a small-plot combine. Grain yields were adjusted to 15.5% moisture before statistical analysis.

Statistical Analysis

The PRE and POST field studies were analyzed separately. Data were subjected to variance analysis using the PROC GLIMMIX procedure in SAS v. 9.4 (SAS Institute, Cary, NC, USA). An initial mixed model analysis was conducted to evaluate site by treatment interactions for all parameters to determine whether data could be pooled across years and locations. The fixed effect for this analysis was herbicide treatment, and the random effects were replication, replication within site, and site by treatment. To pool data, sites were grouped when site by treatment interactions were nonsignificant. Site groups were then subject to a second mixed model analysis to evaluate the effect of herbicide treatment on MHR *A. tuberculatus* control, density, biomass, corn injury, and grain yield. The random effect for this analysis was replication, and the fixed effects were HPPD inhibitor (Factor One), PS II inhibitor (Factor Two), and the two-way interaction of HPPD by PS II inhibitor. The Shapiro-Wilk test and plots of studentized residuals were used to confirm the assumptions of variance analysis (residuals are homogenous, have a mean of zero, and are normally distributed). Visible MHR *A. tuberculatus* control, visible corn injury, and corn yield data were analyzed using a normal distribution. To satisfy the assumptions of variance analysis, a lognormal distribution was used to analyze MHR *A. tuberculatus* density and biomass data. Least-square means for main effects (HPPD inhibitor or PS II inhibitor) were compared when interaction between HPPD inhibitors and PS II inhibitors was nonsignificant. Simple effects were analyzed when the interaction between HPPD inhibitors and PS II inhibitors was significant. Simple effect least-square means were separated using Tukey-Kramer's multiple range test. To present the data, MHR *A. tuberculatus* density, and biomass least-square means and standard errors were back-transformed from the log-scale using the omega method (M Edwards, Ontario Agricultural College Statistician, University of Guelph, personal communication). Colby's equation (Equation 1) was used to calculate expected visible MHR *A. tuberculatus* control and corn injury means for each replication using the observed means for HPPD inhibitor alone (A) and PS II inhibitor alone (B).

$$\text{Expected} = (A + B) - [(A \times B)/100] \quad [1]$$

Expected mean MHR *A. tuberculatus* density and biomass were calculated for each replication using the modified Colby's equation and corresponding nontreated control mean (W) (Equation 2).

$$\text{Expected} = [(A \times B)/W] \quad [2]$$

Observed and expected values were compared using a t-test. If observed and expected values were similar, the interaction was considered additive, and if the values were significantly different, the interaction was classified as either antagonistic or synergistic. A significance level of $\alpha = 0.05$ was used for data analyses; however, significance levels of $\alpha = 0.01$ were noted.

Results and Discussion

HPPD Inhibitors and PS II Inhibitors Applied PRE

Site by treatment interactions were significant for MHR *A. tuberculatus* control, density, biomass, and grain yield with no differences between S1, S4, and S6 or S2 and S5; therefore, data for S1, S4, and S6 were combined and data for S2 and S5 were combined for analysis. Lower MHR *A. tuberculatus* control at S1, S4, and S6 can be attributed to greater MHR *A. tuberculatus* density and biomass in the nontreated control of 890 plants m^{-2} and 171.8 g m^{-2} compared with 35 plants m^{-2} and 68.9 g m^{-2} at S2 and S5 (Tables 3 and 4). Vyn et al. (2006) reported similar differences in MHR *A. tuberculatus* control, which they attributed to variation in *A. tuberculatus* density, biomass, and the resistance profiles of each population. MHR *A. tuberculatus* control can vary due to the resistance profile of each population (Benoit et al. 2019a; Hager et al. 2002; Hausman et al. 2013; Vyn et al. 2006). The number of individual MHR *A. tuberculatus* resistant to each MOA varied by site, with greater resistance to ALS, PS II, and PPO inhibitors at S1, S4, and S6 compared with S2 and S5 (Table 1).

MHR Amaranthus tuberculatus Control

The interaction of HPPD inhibitor by PS II inhibitor, applied PRE, was significant for MHR *A. tuberculatus* control at 2, 4, 8, and 12 WAA (Table 3); therefore, the simple effects are presented (Table 5). At S1, S4, and S6, atrazine, metribuzin, and linuron controlled MHR *A. tuberculatus* 45% to 69%, 69% to 85%, and 82% to 98%, respectively. Linuron controlled MHR *A. tuberculatus* better than atrazine. Isoxaflutole controlled MHR *A. tuberculatus* 58% to 76% across 2, 4, 8, and 12 WAA. The co-application of isoxaflutole with atrazine, metribuzin, or linuron controlled MHR *A. tuberculatus* 80% to 100%. At 8 WAA, the addition of metribuzin or linuron to isoxaflutole increased MHR *A. tuberculatus* control 27% and 33%, respectively, compared with isoxaflutole alone. At 12 WAA, the addition of atrazine, metribuzin, or linuron to isoxaflutole improved MHR *A. tuberculatus* control 22%, 30%, and 34%, respectively. Conversely, the addition of isoxaflutole to atrazine improved MHR *A. tuberculatus* control 24% to 35% at 2, 8, and 12 WAA, and the addition of isoxaflutole to metribuzin improved control 19% at 12 WAA when compared with metribuzin alone. At S1, S4, and S6, the control of MHR *A. tuberculatus* in all herbicide treatments decreased during the course of the growing season, which can be attributed to late-emerging cohorts (Steckel and Sprague 2004).

At S2 and S5, atrazine, metribuzin, and linuron controlled MHR *A. tuberculatus* 87% to 100% and isoxaflutole controlled MHR *A. tuberculatus* 95% to 98% across 2, 4, 8, and 12 WAA. The co-application of isoxaflutole with atrazine, metribuzin, or linuron controlled MHR *A. tuberculatus* 99% to 100%. These results are consistent with those of Hausman et al. (2013), who reported 8% to 58% control of HPPD inhibitor–resistant *A. tuberculatus* 4 WAA with PRE-applied atrazine (1,680 g ha^{-1}). In contrast, Hager et al. (2002) and Hausman et al. (2013) reported metribuzin (420 g ha^{-1}) and linuron (840 g ha^{-1}) applied PRE controlled MHR *A. tuberculatus* up to 92% and up to 58% in soybean [*Glycine max* (L.) Merr.], respectively. Greater *A. tuberculatus* control in this study may reflect the higher application rates of metribuzin (560 g ha^{-1}) and linuron (2,160 g ha^{-1}) compared with Hager et al. (2002) and Hausman et al. (2013), and the more competitive nature of corn.

Results from Colby's equation indicated observed and expected MHR *A. tuberculatus* control were similar for all HPPD- and PS II-inhibitor tank mixtures at all sites and suggests the interaction between isoxaflutole and atrazine, metribuzin, or linuron, applied PRE, is additive for MHR *A. tuberculatus* control. In previous studies, isoxaflutole + atrazine (105 + 1,063 g ha^{-1}) resulted in greater than 97% control of MHR *A. tuberculatus* at 10 WAA (Vyn et al. 2006) and 90% at 12 WAA (Benoit et al. 2019b). Chahal and Jhala (2018) reported variable control of HPPD and PS II inhibitor–resistant *A. palmeri* with isoxaflutole + atrazine that ranged from 14% to 85%; in that study, the interaction between isoxaflutole and atrazine was additive. Additionally, O'Brien et al. (2018) reported an additive interaction between isoxaflutole (105 g ha^{-1}) and metribuzin (191 g ha^{-1}) applied POST for control of an HPPD- and PS II-resistant *A. tuberculatus* population from Nebraska.

MHR Amaranthus tuberculatus Density and Biomass

Averaged across PS II inhibitors, isoxaflutole reduced MHR *A. tuberculatus* density 70% at S1, S4, and S6 (Table 4), which is similar to the 75% density reduction at 4 WAA reported by Hausman et al. (2013). In contrast, there was an interaction between isoxaflutole and PS II inhibitors for MHR *A. tuberculatus* density at S2 and S5 and biomass at all sites (Table 4); therefore, the simple effects are presented (Table 5). At S2 and S5, atrazine, metribuzin, and linuron reduced MHR *A. tuberculatus* density 74%, 100%, and 99%, respectively. Isoxaflutole reduced MHR

Table 3. Least-square means and significance of main effects and interaction for multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* control at 2, 4, 8 and 12 wk after PRE application (WAA) in corn treated with isoxaflutole, PS II inhibitors, and isoxaflutole + PS II inhibitors applied PRE across five field sites in 2019 and 2020 in Ontario, Canada.

		Control[a]							
		2 WAA		4 WAA		8 WAA		12 WAA	
Main effects	Rate	S1, S4, S6	S2, S5	S1, S4, S6	S2, S5	S1, S4, S6	S2, S5	S1, S4, S6	S2, S5
	— g ai ha^{-1} —	%							
Isoxaflutole (g ai ha^{-1})		NS	*	NS	*	NS	*	*	**
0		62	73	62	72	53	72	49	73
79		91	99	90	98	82	98	79	99
SE[b]		3	4	3	4	3	4	3	4
PS II inhibitor treatments		**	**	**	**	**	**	**	**
No tank-mix partner	—	38	47	36	47	31	47	29	49
Atrazine	800	81	97	78	95	66	93	62	96
Metribuzin	560	92	98	90	99	81	100	78	100
Linuron	2,160	97	99	99	99	92	100	87	100
SE[b]		3	4	3	4	3	4	3	4
Two-way interaction									
Isoxaflutole × PS II inhibitor		**	**	**	**	**	**	**	**

[a]Visible MHR *A. tuberculatus* control was evaluated based on plant chlorosis, necrosis, and reduction in plant height relative to the nontreated control, where 0% represented no herbicide injury, and 100% represented complete plant death.
[b]Standard error of the mean.
*Significant (P < 0.05).
**Significant (P < 0.01).
NS, nonsignificant (P > 0.05).

Table 4. Least-square means and significance of main effects and interaction for multiple-herbicide-resistant (MHR) *Amaranthus tuberculatus* density and biomass 4 weeks after PRE application (WAA) and corn grain yield in corn treated with isoxaflutole, photosystem II (PS II inhibitors, and isoxaflutole + PS II inhibitors applied PRE across five field sites in 2019 and 2020 in Ontario, Canada.[a]

		Density		Biomass		Corn yield	
Main effects	Rate	S1, S4, S6	S2, S5	S1, S4, S6	S2, S5	S1, S4, S6	S2, S5
	— g ai ha^{-1}—	plants m^{-2}		g m^{-2}		kg ha^{-1}	
Isoxaflutole (g ha^{-1})		*	**	*	*	NS	NS
0		298 a	10	71.4	10.7	7,900	8,300
79		89 b	0	10.3	0.1	8,800	8,500
SE[b]		39	2	7.1	3.4	300	200
PS II inhibitors		NS	**	**	**	**	NS
No tank-mix partner	—	455	23	109.8	35.7	7,100 b	8,300
Atrazine	800	144	24	45.2	1.9	8,600 a	8,800
Metribuzin	560	78	0	12.3	0	8,700 a	7,800
Linuron	2,160	44	0	3.2	0.1	9,000 a	8,600
SE[b]		39	2	7.1	3.4	300	200
Two-way interactions							
Isoxaflutole × PS II inhibitor		NS	**	**	**	**	NS

[a]Means within same main effect and same column followed by the same letter are not significantly different according to Tukey-Kramer multiple range test (P < 0.05).
[b]Standard error of the mean.
*Significant (P < 0.05).
**Significant (P < 0.01).
NS, nonsignificant (P > 0.05).

A. tuberculatus density 97%, and isoxaflutole + atrazine reduced plant density by 26 percentage points more than atrazine alone.

At S1, S4, and S6, isoxaflutole, metribuzin, and linuron reduced MHR *A. tuberculatus* biomass 78%, 87%, and 97%, respectively; atrazine did not reduce *A. tuberculatus* biomass. The addition of metribuzin or linuron to isoxaflutole reduced MHR *A. tuberculatus* biomass 20% and 21% more than isoxaflutole alone, respectively. The addition of isoxaflutole to atrazine or metribuzin reduced MHR *A. tuberculatus* biomass 42% and 11% more than atrazine or metribuzin alone, respectively. At S2 and S5, atrazine, metribuzin, and linuron reduced MHR *A. tuberculatus* biomass 93% to 100%. Isoxaflutole reduced MHR *A. tuberculatus* biomass 99% and was not improved with the addition of a PS II inhibitor. In contrast, the addition of isoxaflutole to atrazine resulted in 6% greater reductions in MHR *A. tuberculatus* biomass compared with atrazine alone. These results complement those of Vyn et al. (2006), who reported a greater reduction in ALS- and PS II-resistant *A. tuberculatus* density and biomass with isoxaflutole + atrazine that ranged from 92% to 95%, compared with atrazine alone. Results of Colby's analysis indicated additive interactions between isoxaflutole and PS II inhibitors for MHR *A. tuberculatus* density and biomass.

Corn Injury and Grain Yield

Corn injury was not observed with any treatment (data not shown). The lack of corn injury is likely due to the safener, cyprosulfamide, present in the isoxaflutole formulation used in these studies (Robinson et al. 2013; USEPA 2015). There

Table 5. Multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* control at 2, 4, 8 and 12 wk after PRE application (WAA), density, biomass, and grain yield in corn treated with isoxaflutole, photosystem II (PS II) inhibitors, and isoxaflutole + PS II inhibitors applied PRE across five field sites in 2019 and 2020 in Ontario, Canada.

	S1, S4, S6[a]			S2, S5		
	Isoxaflutole rate — g ai ha^{-1} —			Isoxaflutole rate — g ai ha^{-1} —		
	0	79	SE[b]	0	79	SE[b]
Visible control at 2 WAA[c]			%			
No tank-mix partner	0 b Y	76 a Z	9	0 b Y	95 a Z	12
Atrazine	69 a Y	93 a Z (94)[d]	3	95 a Z	99 a Z (100)	1
Metribuzin	85 a Z	98 a Z (98)	2	97 a Z	100 a Z (100)	1
Linuron	96 a Z	98 a Z (100)	1	99 a Z	100 a Z (100)	1
SE[b]	6	2		8	1	
Visible control at 4 WAA						
No tank-mix partner	0 c Y	73 a Z	9	0 b Y	95 a Z	12
Atrazine	65 b Z	91 a Z (90)	4	90 a Y	99 a Z (99)	2
Metribuzin	82 ab Z	97 a Z (96)	2	100 a Z	100 a Z (100)	0
Linuron	98 a Z	100 a Z (100)	1	100 a Z	100 a Z (100)	0
SE[b]	6	3		8	1	
Visible control at 8 WAA						
No tank-mix partner	0 c Y	62 b Z	7	0 c Y	95 a Z	12
Atrazine	50 b Y	81 ab Z (81)	4	87 b Y	99 a Z (99)	2
Metribuzin	73 ab Z	89 a Z (91)	3	100 a Z	100 a Z (100)	0
Linuron	89 a Z	95 a Z (97)	2	100 a Z	100 a Z (100)	0
SE[b]	5	3		8	1	
Visible control at 12 WAA						
No tank-mix partner	0 c Y	58 b Z	7	0 c Y	98 a Z	12
Atrazine	45 b Y	80 a Z (78)	5	93 b Y	100 a Z (100)	1
Metribuzin	69 ab Y	88 a Z (89)	4	100 a Z	100 a Z (100)	0
Linuron	82 a Z	92 a Z (94)	3	100 a Z	100 a Z (100)	0
SE[b]	5	3		8	0	
Density			plants m^{-2}			
No tank-mix partner	890[e]	178	136	35 c Y	1 a Z	5
Atrazine	207	86 (61)	33	9 b Y	0 a Z (0.3)	1
Metribuzin	96	48 (34)	32	0 a Z	0 a Z (0)	0
Linuron	68	32 (44)	15	0.4 a Z	0 a Z (0)	0.3
SE[b]	74	17		3	0.4	
Biomass			g m^{-2}			
No tank-mix partner	171.8 c Y	38.3 b Z	19.5	68.9 c Y	0.4 a Z	11.4
Atrazine	81.9 bc Y	10.9 ab Z (17)	11.6	4.9 b Y	0 a Z (0)	1.5
Metribuzin	22.8 ab Y	3.9 a Z (4)	6.5	0 a Z	0 a Z (0)	0
Linuron	5.7 a Z	1.5 a Z (1)	1.2	0.2 a Z	0 a Z (0)	0.1
SE[b]	12.4	3.4		6.4	0.1	
Corn yield			kg ha^{-1}			
No tank-mix partner	5,100 b Y	8,500 a Z	500	7,300	9,300	600
Atrazine	8,300 a Z	8,900 a Z	500	9,000	8,600	400
Metribuzin	9,000 a Z	9,000 a Z	600	8,000	7,700	500
Linuron	8,800 a Z	8,700 a Z	400	8,900	8,200	400
SE[b]	400	300		300	300	

[a]Within site groupings, means within column followed by the same letter (a–c) or means within row followed by the same letter (Y or Z) are not significantly different according to Tukey-Kramer multiple range test ($P < 0.05$).
[b]Standard error of the mean.
[c]Visible MHR *A. tuberculatus* control was evaluated based on plant chlorosis, necrosis, and reduction in plant height relative to the nontreated control, where 0% represented no herbicide injury and 100% represented complete plant death.
[d]Values in parentheses represent expected values calculated from Colby's analysis.
[e]Interaction was negligible; therefore, only treatment means and results from Colby's analysis are shown.

was an interaction between isoxaflutole and PS II inhibitors for corn grain yield at S1, S4, and S6 (Table 4); therefore, the simple effects are presented (Table 5). Season-long MHR *A. tuberculatus* interference reduced grain corn yield up to 43% or 3,900 kg ha^{-1}. Grain yield reductions at S1, S4, and S6 can be attributed to greater MHR *A. tuberculatus* interference due to greater weed density, biomass, and a greater number of herbicide-resistant individuals compared with S2 and S5, where there was no corn yield loss due to MHR *A. tuberculatus* interference. This is consistent with Vyn et al.'s (2006, 2007) report that corn grain yield differences between herbicide treatments occurred only at sites with greater MHR *A. tuberculatus* pressure and resistance to both ALS inhibitors and PS II inhibitors.

HPPD and PS II Inhibitors Applied POST

Site by treatment interactions were significant for MHR *A. tuberculatus* control, density, biomass, and corn grain yield, with no differences between S1 and S4, or S2, S3, and S5; therefore, for purposes of analysis, data for S1 and S4 were combined and data for S2, S3, and S5 were combined. Lower MHR *A. tuberculatus* control at S1 and S4 can be attributed to greater plant density and biomass in the nontreated control of 463 plants m^{-2} and 69.6 g m^{-2} compared with 54 plants m^{-2} and 50.3 g m^{-2} at S2, S3, and S5 (Table 6). Vyn et al. (2006) reported similar differences in MHR *A. tuberculatus* control, which they attributed to variation in plant density, biomass, and the resistance profiles of the populations under

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Table 6. Least-square means and significance of main effects and interaction for multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* control at 4, 8 and 12 wk after POST application (WAA) in corn treated with 4-hydroxyphenylpyruvate dioxygenase (HPPD), photosystem II (PS II), and HPPD + PS II inhibitors applied POST across five field sites in 2019 and 2020 in Ontario, Canada.

		Control[a,b]					
		4 WAA		8 WAA		12 WAA	
Main effects[c]	Rate	S1, S4	S2, S3, S5	S1, S4	S2, S3, S5	S1, S4	S2, S3, S5
	— g ai ha^{-1} —	%					
HPPD inhibitor		**	**	**	**	**	**
No tank-mix partner	—	17	58	19 b	61	18 b	62
Mesotrione	100	75	97	79 a	98	80 a	99
Tolpyralate	30	69	98	69 a	99	69 a	99
Topramezone	12.5	51	93	53 a	95	53 a	95
SE[d]		2	2	2	2	3	2
PS II inhibitor		**	**	*	**	**	**
No tank-mix partner	—	40	70	41 b	71	41 b	72
Atrazine	560	56	93	59 a	94	59 a	95
Bromoxynil	280	63	94	64 a	96	63 a	96
Bentazon	840	54	90	56 a	92	57 a	93
SE[d]		2	2	2	2	3	2
Interaction							
HPPD inhibitor × PS II inhibitor		*	**	NS	**	NS	**

[a]Means within same main effect and same column followed by the same letter are not significantly different according to Tukey-Kramer multiple range test (P < 0.05).
[b]Visible MHR *A. tuberculatus* control was evaluated based on plant chlorosis, necrosis, and reduction in plant height relative to the nontreated control where 0% represented no herbicide injury and 100% represented complete plant death.
[c]Herbicide treatments with mesotrione included Agral® 90 (Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v); with tolpyralate included methylated seed oil (MSO Concentrate®) (Loveland Products, 3005 Rocky Mountain Avenue, Loveland, CO, USA) (0.5% v/v) and urea ammonium nitrate (UAN 28-0-0) (Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v); and with topramezone included Merge® (BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada) (0.5% v/v).
[d]Standard error of the mean.
*Significant (P < 0.05).
**Significant (P < 0.01).
NS, nonsignificant (P > 0.05).

evaluation. The number of individual MHR *A. tuberculatus* plants resistant to each MOA varied by site, with greater resistance to ALS, PS II, and PPO inhibitors at S1, S3, and S4 compared with S2 and S5 (Table 1). Site by treatment interactions were significant for corn injury. Similar corn injury was observed at S1, S2, and S5; therefore, corn injury data were combined for S1, S2, and S5 for analysis. In contrast, corn injury was not observed at S3 and S4.

MHR Amaranthus tuberculatus Control

There was no interaction between HPPD inhibitors and PS II inhibitors for MHR *A. tuberculatus* control at 8 and 12 WAA at S1 and S4 (Table 6); therefore, the main effects are presented. When averaged across PS II inhibitors, mesotrione, tolpyralate, and topramezone controlled MHR *A. tuberculatus* 79% to 80%, 69%, and 53%, respectively at 8 and 12 WAA. When averaged across HPPD inhibitors, atrazine, bromoxynil, and bentazon controlled MHR *A. tuberculatus* 59%, 63 to 64%, and 56 to 57%, respectively, at 8 and 12 WAA.

There was an interaction between HPPD inhibitors and PS II inhibitors for MHR *A. tuberculatus* control at S1 and S4 at 4 WAA and at S2, S3, and S5 at 4, 8, and 12 WAA (Table 6); therefore, the simple effects are presented (Tables 7 and 8). At S1 and S4, the HPPD inhibitors mesotrione, tolpyralate, and topramezone controlled MHR *A. tuberculatus* 54%, 61%, and 45%, respectively, and the PS II inhibitors atrazine, bromoxynil, and bentazon controlled MHR *A. tuberculatus* 31%, 23%, and 16%, respectively, at 4 WAA. Unacceptable MHR *A. tuberculatus* control with POST-applied PS II inhibitors is consistent with previous studies that report <80% control of MHR *A. tuberculatus* and MHR *A. palmeri* (Anderson et al. 1996; Chahal and Jhala 2018; Corbett et al. 2004; Foes et al. 1998; Hausman et al. 2016; Kohrt and Sprague 2017; Vyn et al. 2006). The addition of atrazine, bromoxynil, or bentazon to mesotrione improved MHR *A. tuberculatus* control 29%, 34%, and 22%, respectively, when compared with mesotrione alone. Similarly, the addition of bromoxynil to tolpyralate increased control 20% when compared with tolpyralate alone. Control of MHR *A. tuberculatus* was not improved with the addition of PS II-inhibiting herbicides to topramezone. Kohrt and Sprague (2017) reported synergistic responses occur more frequently with tank mixtures of atrazine plus triketone HPPD inhibitors, such as mesotrione and tembotrione, compared with the pyrazole HPPD inhibitor topramezone.

Based on Colby's analysis, the improvement in MHR *A. tuberculatus* control with the addition of a PS II inhibitor to a HPPD inhibitor was either additive or synergistic, except topramezone + atrazine, which was antagonistic. These results are consistent with those of Hausman et al. (2011, 2016) and Woodyard et al. (2009), who reported additive or synergistic responses with mesotrione + atrazine and mesotrione + bromoxynil for control of non–herbicide resistant and MHR *A. tuberculatus*. Additionally, Kohrt and Sprague (2017) reported additive or synergistic responses with mesotrione + atrazine, tembotrione + atrazine, tolpyralate + atrazine, and topramezone + atrazine applied POST for MHR *A. palmeri* control.

At S2, S3, and S5, the HPPD inhibitors mesotrione, tolpyralate, and topramezone controlled MHR *A. tuberculatus* ≥95%, ≥97%, and ≥90%, respectively, across 4, 8, and 12 WAA; weed control was not improved by the addition of PS II inhibitors to the HPPD inhibitors. In contrast, the PS II inhibitors atrazine, bromoxynil, and bentazon controlled MHR *A. tuberculatus* ≥79%, ≥83%, and ≥71%, respectively, across 4, 8, and 12 WAA; the addition of HPPD inhibitors to atrazine, bromoxynil, and bentazon improved MHR *A. tuberculatus* control up to 20%, 17%, and 28%, respectively. Similarly, Benoit et al. (2019b) reported greater

Table 7. Least-square means and significance of main effects and interaction for multiple herbicide–resistant (MHR) *Amaranthus tuberculatus* density, biomass and corn injury and corn grain yield in corn treated with 4-hydroxyphenylpyruvate dioxygenase (HPPD), photosystem II (PS II), and HPPD + PS II inhibitors applied POST across five field sites in 2019 and 2020 in Ontario, Canada.

						Corn injury[b]				
		Density[a]		Biomass		S1, S2, S5			Corn yield	
Main effects[c]	Rate	S1, S4	S2, S3, S5	S1, S4	S2, S3, S5	1 WAA	2 WAA	4 WAA	S1, S4	S2, S3, S5
	— g ai ha^{-1} —	—plants m^{-2} —		——— g m^{-2} ———		———— % ————			——kg ha^{-1} ——	
HPPD inhibitor		NS	**	*	**	*	NS	NS	NS	NS
No tank-mix partner		863 a	32 a	206.1 a	24.5 a	2	1	0	4,400	7,300
Mesotrione	100	191 a	2 b	24.2 b	0.6 b	4	1	0	7,900	7,800
Tolpyralate	30	280 a	1 b	37.4 ab	0.2 b	7	3	1	7,300	7,400
Topramezone	12.5	422 a	7 b	80.1 ab	1.7 b	4	1	1	6,600	7,600
SE[d]		36	2	8.8	1.3	0.5	0.2	0.1	200	100
PS II inhibitor		*	*	**	**	**	NS	NS	NS	NS
No tank-mix partner		570 a	19 a	116.9 a	10.9 a	0	0	0	5,800	7,400
Atrazine	560	391 b	4 b	80.2 bc	2.3 b	0	0	0	6,900	7,800
Bromoxynil	280	340 b	3 b	66.6 c	1.5 b	11	4	1	7,000	7,700
Bentazon	840	429 b	10 ab	97.8 b	3.7 ab	5	2	1	6,600	7,300
SE[d]		36	2	8.8	1.3	0.5	0.2	0.1	200	100
Two-way interactions										
HPPD inhibitor × PS II inhibitor		NS	NS	NS	NS	*	NS	NS	*	NS

[a]Means within same main effect and same column followed by the same letter are not significantly different according to Tukey-Kramer multiple range test (P < 0.05).
[b]WAA, weeks after POST application.
[c]Herbicide treatments with mesotrione included Agral® 90 (Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v); with tolpyralate included methylated seed oil (MSO Concentrate®) (Loveland Products, 3005 Rocky Mountain Avenue, Loveland, CO, USA) (0.5% v/v) and urea ammonium nitrate (UAN 28-0-0) (Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v); and with topramezone included Merge® (BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada) (0.5% v/v).
[d]Standard error of the mean.
*Significant (P < 0.05).
**Significant (P < 0.01).
NS, nonsignificant (P > 0.05).

MHR *A. tuberculatus* control with mesotrione + atrazine, tembotrione + atrazine, topramezone + atrazine, and tolpyralate + atrazine compared with atrazine alone. Additionally, Chahal and Jhala (2018) reported greater control of HPPD- and PS II-resistant *A. palmeri* with POST-applied mesotrione + atrazine, tembotrione + atrazine, or topramezone + atrazine compared with each product alone.

Analysis of observed and calculated Colby's expected values indicated the improvement in MHR *A. tuberculatus* control with the co-application of a HPPD inhibitors + PS II inhibitors was additive, except topramezone + bentazon at 4 WAA and topramezone + atrazine at 8 and 12 WAA at S2, S3, and S5, which were antagonistic. Kohrt and Sprague (2017) reported a similar antagonistic response between tolpyralate and atrazine; however, they attributed this response to reduced absorption of tolpyralate due to the high rate of atrazine (35,900 g ha^{-1}). Antagonistic interactions between topramezone and ALS inhibitors have been reported to reduce control of grass weed species; in contrast, this response was not observed in some species when topramezone was co-applied with atrazine (Kaastra et al. 2008). We do not have an explanation for the antagonistic response between topramezone and atrazine or topramezone and bentazon; this response should be evaluated in future studies to determine whether this is a true effect.

MHR Amaranthus tuberculatus Density and Biomass

There was no interaction between the HPPD inhibitors and PS II inhibitors for MHR *A. tuberculatus* density and biomass at 4 WAA (Table 7); therefore, the main effects are presented. At S1 and S4, the HPPD inhibitors, when averaged across the PS II inhibitors, did not reduce MHR *A. tuberculatus* density; the PS II inhibitors, when averaged across the HPPD inhibitors, reduced MHR *A. tuberculatus* density 25% to 40%. At S2, S3, and S5, mesotrione, tolpyralate, and topramezone, when averaged across the PS II inhibitors, reduced MHR *A. tuberculatus* density and biomass 78% to 97%. Atrazine and bromoxynil reduced MHR *A. tuberculatus* density 79% and 84%, respectively, when averaged across HPPD inhibitors.

At S1 and S4, mesotrione reduced MHR *A. tuberculatus* biomass 88% when averaged across PS II inhibitors. When averaged across HPPD inhibitors, atrazine, bromoxynil, and bentazon reduced MHR *A. tuberculatus* biomass 16% to 43%. At S2, S3 and S5, the HPPD inhibitors reduced MHR *A. tuberculatus* biomass 93% to 99% when averaged across PS II inhibitors. When averaged across HPPD inhibitors, atrazine, bromoxynil, and bentazon reduced MHR *A. tuberculatus* biomass 79%, 86%, and 66%, respectively. These findings are consistent with those of Kohrt and Sprague (2017), who reported greater reductions in ALS-, PS II-, and EPSPS-resistant *A. palmeri* with HPPD inhibitors compared with atrazine.

Corn Injury and Grain Yield

There was an interaction between HPPD inhibitors and PS II inhibitors for corn injury at 1 WAA at S1, S2, and S5 (Table 7); therefore, the simple effects are presented. There was no corn injury at S3 and S4 (data not shown). Atrazine did not cause corn injury; however, bromoxynil and bentazon caused 7% and 2% corn injury, respectively (Table 9). Similar corn leaf necrosis was observed at 1 WAA when bromoxynil and bentazon were co-applied with mesotrione, tolpyralate, and tembotrione. Carey and Kells (1995) and Vyn et al. (2006) reported similar early-season corn leaf necrosis with bromoxynil applied POST. Compared with HPPD inhibitors alone, the addition of bromoxynil to mesotrione, tolpyralate, or topramezone increased corn injury 8% to 16%. Similarly, the addition of mesotrione, tolpyralate, or topramezone to bromoxynil increased corn injury 1% to 9%. Observed corn injury at 1 WAA was 5% to 9% greater than the calculated Colby's expected value, indicating a synergistic increase in corn injury with the co-application of tolpyralate and

Table 8. Multiple herbicide–resistant (MHR) Amaranthus tuberculatus control at 4, 8, and 12 wk after POST application (WAA), density, biomass, and corn grain yield in corn treated with HPPD, PSII, and HPPD + PS II inhibitors applied POST across five field sites in 2019 and 2020 in Ontario, Canada.

	Control[a],[b]									
	S1, S4					S2, S3, S5				
Herbicide treatment[c]	No tank-mix partner	Mesotrione	Tolpyralate	Topramezone	SE[d]	No tank-mix partner	Mesotrione	Tolpyralate	Topramezone	SE[d]
Visible control at 4 WAA	%									
No tank-mix partner	0 b Y	54 b Z	61 b Z	45 a Z	4	0 b Y	93 a Z	97 a Z	90 a Z	6
Atrazine	31 a X	83 a Z (69)[e]	63 b YZ (73)	48 a XY (63)**	4	79 a Y	98 a Z (99)	99 a Z (99)	97 a Z (98)	2
Bromoxynil	23 a X	88 a Z (64)**	81 a YZ (70)*	59 a Y (57)	5	83 a Y	100 a Z (99)	99 a Z (99)	95 a YZ (98)	1
Bentazon	16 ab X	76 a Z (61)*	71 ab YZ (67)	53 a Y (54)	5	71 a Y	99 a Z (98)	99 a Z (99)	90 a Z (97)*	3
SE[f]	3	3	2	2		5	0.7	0.3	1	
Visible control at 8 WAA										
No tank-mix partner	0[c]	58	61	45	5	0 c Y	95 a Z	98 a Z	91 a Z	6
Atrazine	35	87 (73)[d]	62 (74)*	52 (65)	4	82 ab Y	99 a Z (199)	99 a Z (100)	97 a Z (99)*	1
Bromoxynil	23	92 (68)**	81 (70)	60 (57)	5	86 a Y	100 a Z (99)	100 a Z (99)	97 a YZ (98)	1
Bentazon	18	81 (66)*	72 (68)	54 (55)	5	75 b Y	99 a Z (99)	99 a Z (99)	94 a Z (97)	2
SE[f]	3	3	3	3		6	0.5	0.3	1	
Visible control at 12 WAA										
No tank-mix partner	0	59	61	44	5	0 c Y	96 a Z	98 a Z	92 a Z	6
Atrazine	34	88 (73)	62 (73)*	53 (63)	5	83 ab Y	99 a Z (99)	99 a Z (100)	97 a Z (99)*	1
Bromoxynil	21	90 (68)**	80 (70)*	59 (56)	5	87 a Y	100 a Z (99)	100 a Z (100)	97 a Z (99)	1
Bentazon	17	83 (66)*	73 (68)	54 (54)	5	77 b Y	99 a Z (99)	99 a Z (99)	94 a Z (97)	2
SE[f]	3	3	3	3		6	0.4	0.3	1	
Density	plants m^{-2}									
No tank-mix partner	863	463	396	578	71	54	11	3	12	6
Atrazine	889	107 (339)	386 (417)	403 (568)	71	20	1 (4.1)	0 (0.8)	3 (7.0)	2
Bromoxynil	811	57 (427)*	146 (414)*	352 (549)	65	19	0 (4.0)*	0 (1.5)	2 (5.0)	2
Bentazon	884	200 (588)	246 (572)	399 (670)	75	35	1 (4.9)	1 (3.1)	12 (13.7)	3
SE[f]	84	42	44.5	54		5	3	0.7	2	
Biomass	g m^{-2}									
No tank-mix partner	247.5	69.6	55.5	108.5	18.8	50.3	2.7	0.7	3.3	4.2
Atrazine	161.3	14.1 (52.0)	59.2 (46.2)	72.5 (81.2)	13.6	13.3	0.2 (1.5)	0.1 (0.1)	1.2 (1.7)	1.0
Bromoxynil	184.7	4.1 (60.2)**	12.9 (50.8)*	55.9 (94.7)	15.5	9.9	0.1 (1.1)	0 (0.2)	0.8 (1.0)	1.1
Bentazon	236.0	18.9 (83.2)*	28.5 (67.4)*	92.0 (123.5)	20.5	20.9	0.2 (0.5)	0.2 (0.2)	2.1 (2.9)	1.9
SE[f]	20.0	6.8	6.8	10.1		4.1	0.4	0.1	0.4	
Corn yield	kg ha^{-1}									
No tank-mix partner	3,800 a Z	6,200 b Z	6,900 a Z	6,300 a Z	300	6,900	8,000	7,100	7,500	300
Atrazine	5,000 a Y	8,600 a Z	7,500 a YZ	6,400 a YZ	300	7,600	8,400	7,400	7,700	300
Bromoxynil	4,300 a Y	8,600 a Z	7,500 a YZ	7,500 a YZ	400	7,700	7,700	7,600	7,700	200
Bentazon	4,300 a Y	8,300 a Z	7,400 a YZ	6,200 a YZ	400	6,900	7,300	7,600	7,400	300
SE[f]	300	200	300	300		300	300	300	300	

[a]Within site groupings, means within column followed by the same letter (a–c) or means within row followed by the same letter (X–Z) are not significantly different according to Tukey-Kramer multiple range test ($P < 0.05$).
[b]Visible MHR *A. tuberculatus* control was evaluated based on plant chlorosis, necrosis, and reduction in plant height relative to the nontreated control, where 0% represented no herbicide injury and 100% represented complete plant death.
[c]Herbicide treatments with mesotrione included Agral® 90 (Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v); with tolpyralate included methylated seed oil (MSO Concentrate®) (Loveland Products, 3005 Rocky Mountain Avenue, Loveland, CO, USA) (0.5% v/v) and urea ammonium nitrate (UAN 28-0-0) (Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v); and with topramezone included Merge® (BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada) (0.5% v/v).
[d]Interaction was negligible; therefore, only treatment means and results from Colby's analysis are shown.
[e]Values in parentheses represent expected values calculated from Colby's analysis.
[f]Standard error of the mean.
*Significant difference of $P < 0.05$ between observed and expected values based on a two-sided *t*-test.
**Significant difference of $P < 0.01$ between observed and expected values based on a two-sided *t*-test.

Table 9. Corn injury due to 4-hydroxyphenylpyruvate dioxygenase (HPPD), photosystem II (PS II), and HPPD + PS II inhibitors applied POST across five field sites in 2019 and 2020 in Ontario, Canada.

	S1, S2, S5				
Herbicide treatment[a,b]	No tank-mix partner	Mesotrione	Tolpyralate	Topramezone	SE[c]
Corn injury at 1 WAA	%				
No tank-mix partner	0 a Z	0 a Z	0 a Z	0 a Z	0.1
Atrazine	0 a Z	0 a Z (0)[d]	0 a Z (0)	0 a Z (0)	0.1
Bromoxynil	7 b X	8 b Y (7)	16 b Z (7)**	13 b YZ (8)*	0.8
Bentazon	2 ab X	6 ab XY (2)	11 b YZ (2)**	2 a X (2)	0.9
SE[c]	0.6	0.8	1.1	0.9	
Corn injury at 2 WAA					
No tank-mix partner	0[e]	0	0	0	0
Atrazine	0	0 (0)	0 (0)	0 (0)	0
Bromoxynil	2	2 (2)	7 (2)**	4 (2)*	0.6
Bentazon	1	3 (1)*	4 (1)*	1 (1)	0.5
SE[c]	0.2	0.3	0.7	0.4	
Corn injury at 4 WAA					
No tank-mix partner	0	0	0	0	0.1
Atrazine	0	0 (0)	1 (0)	0 (0)	0.1
Bromoxynil	1	1 (1)	2 (1)*	1 (1)*	0.3
Bentazon	1	0 (1)	2 (1)	0 (1)	0.2
SE[c]	0.1	0.2	0.3	0.2	

[a]Within site groupings, means within column followed by the same letter (a–c) or means within row followed by the same letter (X–Z) are not significantly different according to Tukey-Kramer multiple range test (P < 0.05). WAA, weeks after POST application.
[b]Herbicide treatments with mesotrione included Agral® 90 (Syngenta Canada Inc., 140 Research Lane, Research Park, Guelph, ON, Canada) (0.2% v/v); with tolpyralate included methylated seed oil (MSO Concentrate®) (Loveland Products, 3005 Rocky Mountain Avenue, Loveland, CO, USA) (0.5% v/v) and urea ammonium nitrate (UAN 28-0-0) (Sylvite, 3221 North Service Road, Burlington, ON, Canada) (2.5% v/v); and with topramezone included Merge® (BASF Canada Inc., 100 Milverton Drive, Mississauga, ON, Canada) (0.5% v/v).
[c]Standard error of the mean.
[d]Values in parentheses represent expected values calculated from Colby's analysis.
[e]Interaction was negligible; therefore, only treatment means and results from Colby's analysis are shown.
*Significant difference of P < 0.05 between observed and expected values based on a two-sided *t*-test.
**Significant difference of P < 0.01 between observed and expected values based on a two-sided *t*-test.

bromoxynil, tolpyralate and bentazon, and topramezone and bromoxynil. Corn injury was transient; less corn injury was observed at 2 and 4 WAA. Transient leaf necrosis caused by bromoxynil is consistent with Cary and Kells (1995) and Vyn et al. (2006), who reported no corn injury at 4 WAA.

There was an interaction between HPPD inhibitors and PS II inhibitors for corn grain yield at S1 and S4 (Table 7); therefore, the simple effects are presented. Greater MHR *A. tuberculatus* density and biomass at S1 and S4 and a greater number of herbicide-resistant individuals resulted in unacceptable control with HPPD inhibitors and PS II inhibitors (Table 8). At S1 and S4, MHR *A. tuberculatus* interference with the HPPD inhibitors and PS II inhibitors applied alone resulted in corn yield that was similar to the weedy control. The addition of atrazine, bromoxynil, or bentazon to mesotrione increased corn grain yield 2,100 to 2,400 kg ha^{-1}. Similarly, the addition of mesotrione to atrazine, bromoxynil, or bentazon increased grain yield 3,600 to 4,300 kg ha^{-1}. These results complement those of Vyn et al. (2006), who reported 3,600 kg ha^{-1} greater corn yield with mesotrione + atrazine compared with atrazine alone.

In summary, these studies identify effective PRE and POST HPPD-inhibitor + PS II-inhibitor tank mixtures that result in season-long control of MHR *A. tuberculatus*. Within MHR *A. tuberculatus* populations, differences in plant density, biomass, and the number of individuals resistant to ALS, PS II, EPSPS, and PPO inhibitors resulted in differences in control. Results from the PRE study indicate linuron is an effective PRE herbicide for control of MHR *A. tuberculatus* in corn. Control of MHR *A. tuberculatus* was greater with PRE applications of isoxaflutole + atrazine, isoxaflutole + metribuzin, and isoxaflutole + linuron compared with each herbicide alone. Isoxaflutole + atrazine, isoxaflutole + metribuzin, and isoxaflutole + linuron are effective PRE tank mixtures that resulted in comparable corn grain yield. Interactions between isoxaflutole and all PS II inhibitors were additive for MHR *A. tuberculatus* control, biomass, and density; however, it is recommended that isoxaflutole be tank mixed with a PS II inhibitor for greater and more consistent MHR *A. tuberculatus* control. Results from the POST study indicate atrazine, bromoxynil, and bentazon controlled MHR *A. tuberculatus* 16% to 87%, while mesotrione, tolpyralate, and topramezone resulted in 45% to 97% control at 4, 8, and 12 WAA. The co-application of HPPD inhibitors and PS II inhibitors applied POST resulted in greater control of MHR *A. tuberculatus* when compared with these products applied alone. Interactions between HPPD inhibitors and PS II inhibitors were mostly additive; however, synergistic responses were observed with mesotrione + bromoxynil, mesotrione + bentazon, and tolpyralate + bromoxynil. It is recommended that POST-applied HPPD inhibitors be tank mixed with a PS II inhibitor for greater control of MHR *A. tuberculatus*. The application of bromoxynil and bentazon resulted in corn injury and was observed as foliar necrosis; however, injury was transient. The co-application of mesotrione + atrazine, mesotrione + bromoxynil, and mesotrione + bentazon resulted in greater corn yield than atrazine alone. We conclude from these studies that the atrazine alternatives metribuzin or linuron can be co-applied with isoxaflutole applied PRE and bromoxynil or bentazon can be co-applied with mesotrione or tolpyralate applied POST for control of MHR *A. tuberculatus*; these tank mixtures exhibit complementary activity and provide excellent season-long control of MHR *A. tuberculatus* in corn. Weed management programs often incorporate HPPD inhibitors and PS II inhibitors; future research should focus on the determination of other alternative HPPD-inhibitor tank-mixture partners, complementary herbicide tank mixtures, and integrated weed management strategies to reduce selection for

HPPD inhibitors and PS II inhibitor–resistant biotypes. The ability of *A. tuberculatus* to rapidly evolve resistance to multiple effective herbicide MOAs, including the HPPD inhibitors, warrants the use of diverse weed management strategies.

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